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**Adopting the Therapeutic Orphan? A Legal and Regulatory
Assessment of the FDA's Pediatric Testing Rule**

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Introduction

The central purpose of the prescription drug provisions of the Food Drug & Cosmetic Act¹ (FDCA) is to ensure the public health by verifying the safety and efficacy of all pharmaceuticals that come to market.² The Food and Drug Administration (FDA) achieves this purpose primarily by requiring extensive premarket testing of all prescription drugs for safety and efficacy. Yet one distinct demographic group has not shared in the protections intended by the FDCA: children.³ Drugs prescribed for children are overwhelmingly untested in pediatric populations, and their safety and efficacy are generally inferred only by extrapolating from adult clinical trials through pharmacokinetic or pharmacodynamic analyses. As a result, pediatricians across the country are put in the difficult quandary of having either to prescribe a potentially imprecise therapeutic regime for their patients or to withhold potentially beneficial treatment.⁴ In order to address this problem, FDA issued a final rule in 1998 that authorizes it to mandate pediatric testing of all new drugs for their claimed indications and of any marketed drug or biological product that is “used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over

¹Federal Food, Drug and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301 et seq. (1996)).

²See, e.g., *United States v. An Article of Drug, Bacto-Unidisk*, 394 U.S. 784, 789 (1969).

³The authors of the FDCA clearly intended to include children within the statute’s protections. As one of its main sponsors succinctly stated: “[T]he purpose of [the FDCA] is to protect the public, to protect the mothers and the children....” 81 CONG. REC. 7312 (1937 (statement of Rep. Coffee)).

⁴See Committee on Drugs, American Academy of Pediatrics, *Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations*, 95 PEDIATRICS 286 (1995) (describing this decision as an ethical dilemma no less difficult than the decision whether to test on pediatric subjects).

existing treatments for pediatric patients”⁵ (“the Pediatric Testing rule,” “the 1998 rule”). This rule empowers FDA to require a manufacturer to conduct clinical tests on children to ensure (1) the safety and efficacy in children of all new drugs; and (2) the safety and efficacy of prevalent off-label pediatric uses of existing drugs, regardless of whether the manufacturer intended to market the drug for pediatric use.

The Pediatric Testing rule—particularly as it applies to already-marketed drugs—is dramatic in two ways. First, it represents a substantial step toward including pediatric patients under the aegis of the FDCA’s substantive protections. At the same time, however, the rule also represents an enormous expansion of FDA’s regulatory authority and self-understanding. Until the rule, FDA’s role was limited to ensuring the safety and efficacy of all drugs *based on the use intended by the manufacturer*. Manufacturers retained control over the indications and populations for which the drug would be labeled and marketed. By contrast, this new regulation allows FDA to mandate testing of already-marketed drugs for use in populations wholly unintended—even disclaimed—by the manufacturer.

This paper explores the legality and the proper limits of the FDA’s rule. Part I lays out the background for the rest of the paper by exploring the complicated policy and ethical problems posed by inadequate pediatric research. Part II describes the history of FDA’s response to the problem of inadequate pediatric information, culminating in the 1998 rule. Part III describes the 1998 rule’s

⁵21 C.F.R. §201.23(a) (1999).

potentially dramatic expansion of FDA’s power over the regulated pharmaceutical industry and analyzes whether this expansion falls within the agency’s statutory authority under the FDCA. Part IV explores the legislative history behind the recently passed Food and Drug Administration Modernization Act of 1997⁶ (FDAMA) and suggests that Congress, when confronted with the 1998 Pediatric Testing rule, intended to relegate it to a policy of last resort. As a result, congressional passage of the FDAMA should limit the rule’s application to the fairly narrow set of circumstances, described in Part V, in which market incentives are inadequate to induce sufficient pediatric testing. Ultimately, although the Pediatric Testing rule is a valid exercise of administrative authority, the legislative backdrop for the rule should caution FDA against imposing the mandate except as a means of correcting “market failure.”

I. ADOPTING THE THERAPEUTIC ORPHAN—THE NEED FOR PEDIATRIC TESTING

A. THE CONSEQUENCES OF INADEQUATE PEDIATRIC RESEARCH

Despite the substantive protections of the FDCA, an overwhelming proportion of the drugs prescribed by physicians to children have never been tested in pediatric patients or approved by FDA for their use. Clinical trial data submitted to FDA as part of a New Drug Application (NDA) typically does not

⁶Food and Drug Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

include data from pediatric testing but is rather limited to clinical tests on adult subjects. Phase I and II clinical trials generally are limited to adult (usually male) subjects between ages 20 and 40; Phase III trials often include a wider range of age groups, including the elderly, but children—particularly infants—are usually not included.⁷

As a result of these clinical testing standards, most drugs approved by FDA are labeled with disclaimers against pediatric use. According to the 1991 edition of the Physician's Desk Reference (PDR), 81% of all prescription drugs contained language disclaiming use in children;⁸ an even greater number disclaimed use in infants, for whom almost no information is currently available.⁹ A survey of new molecular entities (NMEs) by FDA from 1984 to 1989 similarly found that 80% were approved without labeling for pediatric use.¹⁰ In 1992, only two out of nineteen drugs (11%) approved by FDA were labeled for pediatric use;¹¹ in 1995, only four out of twenty-five (16%) were so labeled.¹² Many of these drugs have significant therapeutic use for pediatric populations. For example, pediatric use of most of the drugs commonly used to treat pain in children—e.g., morphine, meperidine, fentanyl, midazolam, bupivacaine, and ketorolac—is explicitly disclaimed by the manufacturer.¹³ Some drugs—such as the asthma

⁷ See Charles J. Cote, Ralph E.. Kauffman, Gloria J. Troendle & George H. Lambert, *Is the "therapeutic orphan" about to be adopted? Use of nonpediatric-approved drugs on children*, 98 PEDIATRICS 118 (1996).

⁸ See J. T. Gilman & P. Gal, *Pharmacokinetic and pharmacodynamic data collection in children and neonates*, 23 CLINICAL PHARMACOKINETICS 1 - 3 (1992); see also 143 CONG. REC. E1093 (daily ed. June 3, 1997) (statement of Rep. Waxman).

⁹ See Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,632 (1998).

¹⁰ See CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, OFFICES OF DRUG EVALUATION STATISTICAL REPORT (1989).

¹¹ See Committee on Drugs, American Academy of Pediatrics, *Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations*, 95 PEDIATRICS 286 (1995).

¹² See 142 CONG. REC. S11,992 (daily ed. Sept. 30, 1996, statement of Sen. Kassebaum).

¹³ See Charles J. Cote, Ralph E.. Kauffman, Gloria J. Troendle & George H. Lambert, *Is the*

drug Albuterol—are used primarily in children but yet are not approved for pediatric use.¹⁴ Finally, the issue of inadequate pediatric research has been brought to the fore by the epidemic of pediatric AIDS. Although medical advances such as protease inhibitors and new cocktail drugs have raised the hope that AIDS victims will live longer, healthier lives, none of these drugs has been approved for use in newborns or infants, despite the fact that the first days of life may provide the best opportunity for reversing the effects of HIV.¹⁵

To be sure, some of these drugs are indirectly tested through the use of studies that extrapolate from adult tests in order to infer the safety and efficacy of drugs on children. But, especially for infants, these tests are frequently inaccurate because “[g]rowth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in newborn, infant, child, or adolescent as compared to adult.... Drug studies in adult humans may not adequately predict the pharmacokinetic, pharmacodynamic, or toxic properties of drugs, in children.”¹⁶ Extrapolation from adult studies is at best an inexact science, since it provides no real guarantee that the distinctive physiology of children will not cause adverse reactions to the drug in children.

“therapeutic orphan” about to be adopted? Use of nonpediatric-approved drugs on children, 98 PEDIATRICS 118, 119 (1996)..

¹⁴Although asthma is the single most common reason for admissions to the hospital of children under five, no asthma drug on the market is actually approved for use in patients under five. See 143 CONG. REC. S4277 (daily ed. May 9, 1997, statement of Sen. Dodd).

¹⁵See 143 CONG. REC. S4277 (daily ed. May 9, 1997, statement of Sen. Dodd). The absence of AIDS drugs approved for pediatric use has created a dilemma for many HIV-infected parents. As one commentator to the FDA’s Pediatric Testing Rule noted, “the absence of drugs for [HIV] infection that are appropriately labeled and formulated for pediatric patients causes parents to give children inappropriate doses, sometimes giving up part of their own dose if the child’s physician will not prescribe it.” Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,637 (1998).

¹⁶Committee on Drugs, American Academy of Pediatrics, *Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations*, 95 PEDIATRICS 286 (1995).

The result of this systematically inadequate pediatric labeling is that off-label prescribing by physicians has “by default become an established standard of care of children.”¹⁷ Pediatricians must, through a combination of guesswork and extrapolation from information gleaned from studies of adults, estimate the proper therapeutic regimen for their pediatric patients. While such off-label prescriptions are explicitly lawful,¹⁸ they create significant risks to the health of pediatric populations. These dangers are not just theoretical but real: Drugs that have been administered to children without sufficient pediatric testing have resulted in severe toxic effects, including fatalities.¹⁹ Perhaps the most widely-recognized example is the death of a number of newborn infants in the 1950s as a result of “gray-baby” syndrome induced by chloramphenicol, which was never tested for safety and efficacy in neonates.²⁰ More recent examples include toxicities experienced in the pediatric use of common drugs such as bupivacaine,²¹

¹⁷ See 143 CONG. REC. S11,992 (daily ed. Sept. 30, 1996, statement of Sen. Kassebaum) (quoting the American Academy of Pediatrics).

¹⁸ Indeed, the FDAMA explicitly amended the FDCA to prohibit the FDA from interfering in the practice of medicine by physicians. See Pub. L. No. 105-115, § 214, 111 Stat. 2296, 2348 (codified at 21 U.S.C. § 396 (1997 Supp.)).

¹⁹ See, e.g., W. A. Silverman, D. H. Anderson, W. A. Blanc & D. N. Crozier, *A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic regimens*, 18 PEDIATRICS 614 (1956).

²⁰ See L. E. Bums, J. E. Hodgman & A. B. Cass, *Fatal circulatory collapse in premature infants receiving chloramphenicol*, 261 NEW ENG. J. MED. 1318 - 1321 (1959); H. M. Feder, Jr., C. Osier & E. G. Maderazo, *Chloramphenicol: a review of its use in clinical practice*, 3 REV. INFECTIOUS DISEASE 479 - 91 (1981); D. A. Powell & M. C. Nahata, *Chloramphenicol: New Perspectives on an Old Drug*, 16 DRUG INTELLIGENCES & CLINICAL PHARMACY 295 - 300 (1982).

²¹ See R. Agarwal, et. al., *Seizures Occurring in Pediatric Patients Receiving Continuous Infusion of Bupivacaine*, 75 ANESTHESIA & ANALGESIA 1305 - 06 (1993); J. J. McCloskey, et. al., *Bupivacaine Toxicity Secondary to Continuous Caudal Epidural Infusion in Pediatric Patients*, 75 ANESTHESIA & ANALGESIA 287 - 90 (1992).

vecuronium,²² midazolam,²³ and fentanyl.²⁴ These fatalities and adverse reactions could be eliminated by ensuring that drugs used in children are properly tested in pediatric populations.

B. THE ETHICAL DILEMMA OF PEDIATRIC TESTING

While inadequate information clearly poses risks to pediatric patients, pediatric testing poses risks of its own. As a result, it is perhaps on an ethical rather than a legal level that FDA's rule is most controversial. As part of its argument that the Pediatric Testing rule is authorized by the FDCA, FDA argues that the rule is authorized by § 505(i), which allows FDA to make exceptions to its normal regulations for the purpose of allowing investigations of new drugs, and by § 505(k), which requires FDA to have "due regard... for the interests of patients" subject to those investigational drugs. Together, FDA argues, these provisions allow it to "impose conditions on the investigation of new drugs, including conditions related to the ethics of a proposed investigation and to the

²²See D. M. Fisher et. al., *Neuromuscular Effects of Vecuronium (ORG NC45) in Infants and Pediatric Patients During N₂O Halothane Anesthesia*, 58 ANESTHESIOLOGY 519 - 23 (1983).

²³See A. Hiller, et. al., *Unconsciousness Associated with Midazolam and Erythromycin*, 65 BRIT. J. ANAESTHESIA 826 - 28 (1994); K. T. Olkkola, et. al., *A Potentially Hazardous Interaction Between Erythromycin and Midazolam*, 53 CLINICAL PHARMACY THERAPY 298 - 305 (1993).

²⁴See I. S. Gauntlett, *Pharmacokinetics of Fentanyl in Neonatal Humans and Lambs: Effects of Age*, 69 ANESTHESIOLOGY 683 - 87 (1988); R. E. Kauffman, *Fentanyl, Fads, and Folly: Who Will Adopt the Therapeutic Orphans?*, 119 J. PEDIATRICS 588 - 89 (1991); G. Koren et. al., *Unexpected Alterations in Fentanyl Pharmacokinetics in Pediatric Patients Undergoing Cardiac Surgery: Age Related or Disease Related?*, 9 DEVELOPMENTAL PHARMACOLOGY THERAPEUTICS 183 - 91 (1986).

interests of patients.”²⁵ In the context of pediatric drugs, “[b]ecause exclusion of pediatric patients from clinical trials may deny them an equitable share of the benefits of research, [these provisions] authorize FDA to require their inclusion in clinical trials.”²⁶ In short, FDA argues that the ethical treatment of children requires the Pediatric Testing rule.

Notwithstanding FDA’s claim to be defending the best interests of pediatric patients, there is considerable disagreement as to whether it is inclusion or exclusion that is ethically problematic. On one side, it is clear that the exclusion of pediatric patients from clinical trials denies the group as a whole the benefits of scientific research. Pediatricians and children’s advocates, agreeing with FDA, have been vocal in condemning this exclusion as unethical. For example, the American Academy of Pediatrics has consistently called for pediatric testing, citing “a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents.”²⁷ Indeed, some children’s advocates have gone so far as to suggest—albeit quite implausibly—that the exclusion of children from clinical testing rises to the level of a violation of the Equal Protection Clause.²⁸ In sum, advocates of pediatric

²⁵Proposed Pediatric Testing Rule, 62 Fed. Reg. 43,900, 43,908 (1997).

²⁶*Id.*

²⁷Committee on Drugs, American Academy of Pediatrics, *Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations*, 95 PEDIATRICS 286 (1995).

²⁸See Althea Gregory, *Denying Protection to those Most in Need: The FDA’s Unconstitutional Treatment of Children*, 8 ALB. L.J. SCI. & TECH. 121, 134 - 147 (1997). The argument is implausible because the Supreme Court has consistently rejected the proposition that age is a suspect classification under the Equal Protection Clause. For its most recent reaffirmation, see *Kimel v. Florida Board of Regents*, __ U.S. __, 2000 WL 14165 (Jan. 11, 2000) (reaffirming that “age is not a suspect classification under the Equal Protection Clause” and striking down the ADEA, as applied to state government employers, as an invalid exercise of congressional power under § 5 of the 14th Amendment). Although the Court’s holdings have occurred in the context of *old* age, the Court’s rationales—that age is relevant to state interests and therefore does not create an inference of prejudice or antipathy—apply equally to discrimination against children and infants. Cf. *infra* note 38.

testing argue that the exclusion of pediatric patients is distributively unfair to children *as a group* because it denies them the benefits of more thorough clinical research.²⁹

There are powerful arguments on the other side, however, mainly grounded in the rights-based notion that it is never justified to put an individual at risk, even in order to advance medical knowledge.³⁰ This problem arises with full force in the context of controlled clinical trials—widely used to establish the efficacy of a drug in pediatric populations—which must generally be controlled by administering placebos to a control group. Especially when the pediatric patient suffers from a serious condition, being placed in a control group poses risks to that patient’s health in order to advance the good of the pediatric population as a whole. Although proponents of pediatric testing, including FDA, have attempted to develop ethical guidelines for clinical testing in order to reduce the risks to the individual pediatric patient, no guidelines have completely eliminated the fact the individual patient’s welfare may be subordinated to the welfare of pediatric patients as a whole.³¹ As the current Department of Health

In addition, any equal protection claim would fail given that FDA has not intentionally discriminated against pediatric patients. Rather, such discrimination is merely the effect of a general policy of only reviewing data and representations produced by the manufacturer. Because disparate impact is not sufficient to establish an equal protection violation, *see* *Washington v. Davis*, 426 U.S. 229 (1976), any claim against FDA’s previous pediatric testing policy would fail.

²⁹*See* Proposed Pediatric Testing Rule, 62 Fed. Reg. 43,900, 43,908 (1997) (“Fairness in distribution of the burdens and benefits of research is one of the ethical principles underlying federal regulations on investigational drugs.”); Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,192, 23,194 (1979) (same).

³⁰For the most well-known argument to this effect, *see* PAUL RAMSEY, *THE PATIENT AS PERSON* (1970).

³¹*See* Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,655 (1998) (“[A]lternatives to placebo-controlled trials should be used wherever they can provide sufficient information to establish effectiveness.”); *see also* 21 C.F.R. § 314.126 (1999) (allowing data from active control studies for certain therapeutic classes such as anti-infectives and oncologic drugs); *see also* Committee on Drugs, American Academy of Pediatrics, *Guidelines for the ethical conduct*

and Human Services guidelines prescribe, placebo-controlled studies may be conducted, even to the potential detriment to the subject, if “[t]he intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition.”³²

Pediatric testing also raises a complex problem regarding the relationship between parental authority and the child’s individual autonomy. Traditionally, young children (as contrasted to adolescents, who have been granted some independence from their parents³³) are considered, because of their limited competence to consent, to be exclusive wards of their parents, who have the authority and duty to make decisions on their behalf.³⁴ Thus for those children who, in the judgment of the Institutional Review Board (IRB) overseeing the study, are not mature enough to give their assent to clinical testing, FDA requires permission of the child’s parent or guardian.³⁵ The substitution of parental

of studies to evaluate drugs in pediatric populations, 95 PEDIATRICS 286 (1995) (prescribing limits on the ethical use of placebo control groups); *see also* NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH INVOLVING CHILDREN, REPORT AND RECOMMENDATIONS: RESEARCH INVOLVING CHILDREN (1977); K. Lebacqz, *The National Commission and research in pharmacology: an overview*, 36 FED. PROC. 2344 - 48 (1977) (recommending special protections for vulnerable and noncomprehending subjects).

³²Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9814, 9819 (1983) (codified in 45 C.F.R. § 46.406 (1999)).

³³The ethical problems involving adolescents and young adults are quite different from those involving children who are clearly unable to give meaningful consent. Obviously, the line between the two groups is somewhat hazy. *See, e.g.*, *Planned Parenthood of Missouri v. Danforth*, 428 U.S. 52 (1976) (A minor can give effective consent if she is “sufficiently mature to understand the procedure and to make an intelligent assessment of her circumstances with the advice of a physician.”). But when a child is considered sufficiently mature to consent, the legal quandary usually arises when the child’s legal will differs from that of her parents. *See, e.g.*, *Bonner v. Moran* 126 F.2d 121 (D.C. Cir. 1941).

³⁴The most famous cases arise in the context of parents’ constitutional right to control their children’s education. *See Wisconsin v. Yoder*, 406 U.S. 205 (1972); *Pierce v. Society of the Sisters of the Holy Names of Jesus and Mary*, 268 U.S. 510 (1925); *Meyer v. Nebraska*, 262 U.S. 390 (1923).

³⁵*See* Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9814, 9819 (1983) (codified in 45 C.F.R. § 46.408 (1999)).

consent raises the obvious specter of conflicts between the best interests of the child and potential ulterior interests of the parent. For example, in cases where compensation is given for participation in the study, parents may be induced to assent to their child's participation without full reflection on the study's risks and benefits. In addition, research has shown that "parents who volunteer their children for medical research are significantly more socially disadvantaged and emotionally vulnerable" than those who do not.³⁶ Poor and minority children are also overrepresented in research protocols.³⁷ Thus, the inclusion of children itself raises serious questions of distributive fairness and equity.³⁸

Nevertheless, as a majority of experts in the field of medical ethics agree,³⁹ the benefits of pediatric testing outweigh the risks to pediatric subjects for three basic reasons. First, the risks posed by controlled clinical tests, which can be minimized through the use of appropriate ethical and medical standards, pale in comparison to the risks posed by unregulated off-label experimentation by physicians. Second, even if the risks of nonvalidated drug treatment are the same in controlled and uncontrolled settings, clinical trials are preferable

³⁶See S. C. Harth & Y. H. Thong, *Sociodemographic and Motivational Characteristics of Parents Who Volunteer Their Children for Clinical Research: A Controlled Study* 300 BRIT. J. MED. 1372 - 76 (1990) (finding that only 15 percent of mothers and 16 percent of fathers who volunteered their children had a university education while 26 percent of mothers and 45 percent of fathers who did not volunteer their children had a university education).

³⁷See, e.g., A. S. TANNENBAUM & R. A. COOKE, RESEARCH INVOLVING CHILDREN app. 1 - 10 (1997).

³⁸Arguably, this inequality is more constitutionally serious than the inequality created by inadequate pediatric testing because minority children—who are a constitutionally suspect class—are disproportionately disadvantaged by the current clinical testing regime. *Cf. supra* note 28.

³⁹See, e.g., NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH INVOLVING CHILDREN, REPORT AND RECOMMENDATIONS: RESEARCH INVOLVING CHILDREN (1977); Committee on Drugs, American Academy of Pediatrics, *Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations*, 95 PEDIATRICS 286 (1995).

because they allow researchers to accumulate new information that may aid future patients. Finally, the risks posed to individual pediatric subjects are less ethically problematic than the risks posed by inadequate pediatric information: Whereas participants in any clinical study must give informed consent, either directly or through their parents, children who receive nonvalidated prescription drugs are totally defenseless against the risks posed by untested drugs. Thus, although there are countervailing arguments, it is not “arbitrary and capricious” for FDA to conclude that pediatric testing is ethically justified.

II. THE ORIGINS OF FDA’S PEDIATRIC TESTING RULE

Startled by the inadequacy of pediatric information in prescription drug labeling, FDA promulgated a series of rules over the course of half a decade designed to rectify the paucity of pediatric testing of prescription drugs. Through these regulations, which culminated in the 1998 Pediatric Testing Rule, FDA gradually expanded its authority to allow it to mandate pediatric testing by pharmaceutical companies.

FDA’s initial response in 1992 was to propose a rule amending the agency’s “pediatric use” labeling requirements.⁴⁰ As finalized in 1994,⁴¹ the rule represented a two-pronged effort to foster greater information about the pediatric uses of prescription drugs. First, it relaxed the clinical test requirements for

⁴⁰See Proposed Pediatric Use Labeling Rule, 57 Fed. Reg. 47,423 (1992) (amending the previous requirements, 44 Fed. Reg. 37,434 (1979) (codified at 21 C.F.R. 201.57(f)(9) (1999))).

⁴¹See Pediatric Use Labeling Rule, 59 Fed. Reg. 64,240, 64,241 (1994).

pediatric labeling by allowing manufacturers to label drugs for pediatric use based “on adequate and well-controlled studies in adults together with other information supporting pediatric use (e.g., pharmacokinetic data, safety data, pharmacodynamic data)” instead of based on actual clinical tests on children.⁴² Since extrapolation from adult studies is substantially cheaper and less time-consuming than full-blown pediatric clinical trials, the regulation was designed to reduce the cost to manufacturers of obtaining pediatric information. In addition, the regulation increased the cost of *not* performing pediatric analyses by imposing a disclaimer or warning requirement on drugs for which pediatric information is inadequate. According to the regulation, if there is not “substantial evidence to support any pediatric use or use in a particular pediatric population,” the “Pediatric use” section of the label must contain a disclaimer stating that “Safety and effectiveness in pediatric patients have not been established.”⁴³ If there is a specific hazard associated with the product, the rule imposes a warning requirement in the “Contraindications” section of the label.⁴⁴

Although the rule was designed to create greater incentives for manufacturers to test and label drugs for pediatric use, the 1994 rule did not immediately solve the problem of inadequate pediatric testing. Three years after the rule was finalized, FDA conducted a study that compared the number of NMEs that were approved in 1991 and 1996 and found that the number of NMEs that provided adequate pediatric labeling had dropped from 56% (nine out of sixteen) to

⁴²*Id.* at 64,241.

⁴³*Id.* at 64,240.

⁴⁴*See id.*

38% (fifteen out of forty).⁴⁵ In addition, it found that manufacturers' voluntary promises to conduct pediatric tests had not "substantially increased the number of products entering the marketplace with adequate pediatric testing."⁴⁶ Rather, these promises went unkept, largely because FDA lacked any power to enforce them. In short, FDA concluded that the voluntary regime instituted by the 1994 rule had not succeeded.

As a result, in 1997, FDA issued a rule allowing it to mandate pediatric testing. The rule is two-pronged. First, the rule establishes a presumption that all new drugs and biological products will be studied in pediatric patients, but allows manufacturers to obtain a waiver if they can show that the product will provide no meaningful therapeutic advance for pediatric patients.⁴⁷ The rule also allows companies to request deferral of pediatric testing for not-yet-approved products until safety and effectiveness have been demonstrated in adult populations.⁴⁸ Consistent with the 1994 rule, extrapolation from adult studies rather than clinical trials on pediatric subjects may, at FDA's discretion, be deemed to satisfy the testing requirement.⁴⁹ Moreover, the rule does not require a manufacturer of a new drug or biological product to study its product for unapproved or off-

label indications, even if the product is widely used in pediatric patients for

⁴⁵See Proposed Pediatric Testing Rule, 62 Fed. Reg. 43,900, 43,902 (1997); Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,638 tbl. 1 (1998).

⁴⁶Proposed Pediatric Testing Rule, 62 Fed. Reg. 43,900, 43,902 (1997); see Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,638 tbl. 1 (1998) (showing that between 1991 and 1996 only 11 out of 64 promises to conduct postapproval pediatric tests actually led to the addition of pediatric labeling).

⁴⁷See Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,634 (1998) (codified at 21 C.F.R. 314.55 (1999)).

⁴⁸See *id.* at 66,634 - 35.

⁴⁹See *id.*

those indications.⁵⁰ Second, in terms of already marketed products, the rule allows FDA to require pediatric testing of any marketed drug or biologic that is “used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients.”⁵¹ FDA may require pediatric testing of these drugs even if the manufacturer did not intend to market them for pediatric use.⁵²

Thus, over the course of the decade, FDA initiated a voluntary testing and labeling program and followed it up with a mandatory testing program. In analyzing this historical progression, it is important to understand how the 1994 voluntary testing rule legitimized the 1998 rule. First, the 1994 rule validated the 1998 rule by allowing FDA to argue that the voluntary testing requirement—which had been in place for only a few years—had failed to achieve its intended goal.⁵³ By experimenting with an incentive scheme, but arguably never giving it a real chance to work, FDA artificially enhanced its justification for the testing requirement. Second, the 1994 rule explicitly paved the legal way for the 1998 rule. In its 1994 rule, FDA included dictum stating that it had the legal authority to require pediatric testing, even though it was creating only a voluntary scheme.⁵⁴ The 1998 rule explicitly cited this dictum in support of FDA’s authority to promulgate the testing requirement.⁵⁵ Thus, the most important aspect of the 1994 rule was not its efficacy in inducing increased pediatric test-

⁵⁰ *See id.*

⁵¹ 21 C.F.R. §201.23(a) (1999).

⁵² *See* Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,634 (1998).

⁵³ *See* Pediatric Testing Rule, 63 Fed. Reg. at 66,632 (“The response to the 1994 rule has not substantially addressed the lack of adequate pediatric use information for marketed drugs and biological products.”).

⁵⁴ *See* Pediatric Use Labeling Rule, 59 Fed. Reg. at 64,242 - 43.

⁵⁵ *See* Pediatric Testing Rule, 63 Fed. Reg. at 66,657.

ing but rather its significance as the foundation for FDA's later assertion of statutory authority to mandate pediatric studies.

III. A LEGAL AND REGULATORY ANALYSIS OF FDA'S PEDIATRIC TESTING RULE

The 1998 Pediatric Testing rule was a dramatic step in FDA's efforts to enhance children's health. Not surprisingly, commentators have questioned whether the agency's expansion of power is authorized by law. This Part provides an analysis of the legality of FDA's rule, as well as of its relationship to the FDAMA. I conclude that FDA's Pediatric Testing Rule is indeed authorized by the broad language of the FDCA and is not "arbitrary and capricious" in violation of the APA. However, although the Pediatric Testing rule represents a potentially dramatic expansion of FDA's power over industry, Congress's enactment of the FDAMA means that FDA should not invoke the testing requirement except in cases where the incentives created by Congress have demonstrably failed.

A. FDA AND INDUSTRY—A RADICAL TRANSFORMATION

The 1998 rule undoubtedly represents a dramatic expansion of FDA’s regulatory authority. Until the Pediatric Testing Rule, FDA’s primary regulatory responsibility was to ensure that drugs were safe and efficacious for the indications for which they were intentionally marketed. Under this regime, manufacturers controlled both the marketing of their product and the testing of the drug; consequently, they could avoid costly testing by declining to market the product for a particular indication or subpopulation.⁵⁶ The role of FDA was simply to assess the proposed marketing in light of data provided by the manufacturer and submitted to FDA. As FDA stated in 1967, “it is the manufacturer who chooses the indications to be investigated and determines the dosage level for which he will seek FDA approval. It is the duty of the Food and Drug Administration under the law to decide that proposed usages and levels are both safe and effective, based on the data submitted by the manufacturer.”⁵⁷ By requiring manufacturers to conduct and submit pediatric testing—even if the manufacturer would prefer to disclaim pediatric use of the product—FDA dramatically increased its authority over drug manufacturers.

The obvious question is whether this expansion of power is authorized by the FDCA. Even some FDA officials have expressed concern in the past that such a provision is unauthorized. As then-FDA Commissioner David Kessler remarked in a 1992 speech: “Despite the ardent desire of FDA to increase pediatric indications, I need to acknowledge the limits of FDA’s authority. It is our job to

⁵⁶ See S. REP. NO. 361, 74th Cong., at __ (1937) (“The manufacturer of the article through his representations in connection with its sale, can determine the use to which the article is to be put.”).

⁵⁷ See Pharmaceutical Research and Manufacturers of America, *Comment on Proposed Pediatric Testing Rule*, No. 97N-0165, Nov. 13, 1997.

review drug applications for the indications suggested by the manufacturer. We do not have authority to require manufacturers to seek approval for indications which they have not studied.... Thus, as a matter of law, if an application contains indications only for adults, we're stuck.”⁵⁸ Through the 1998 rule, FDA attempted to unstick itself; but did it do so legally?

Before delving into the particular statutory claims made by FDA, it is important to review the general interpretive framework that the courts have adopted in construing FDA authority under the FDCA. As a matter of administrative law, the 1998 rule may be challenged either as a statutorily unauthorized exercise of agency power (*Chevron*⁵⁹) or as an “arbitrary and capricious”⁶⁰ exercise of administrative discretion (*Overton Park*⁶¹). Because FDA serves such an important public function—namely protecting human health and safety—its power—especially under § 701(a) of the FDCA—has been broadly construed.⁶² To borrow a constitutional analogy, § 701(a) has been interpreted as analogous to a “necessary and proper clause,” whereby “the validity of a regulation promulgated [under the Act] will be sustained so long as it is ‘reasonably related to the purposes of [the Act].’”⁶³ Thus, as long as the regulation is designed to satisfy a congressional objective that is expressed somewhere in the FDCA, the regulation will be upheld.⁶⁴ As the following analysis demonstrates, only one of

⁵⁸Commissioner David Kessler, Speech, *cited in* Pharmaceutical Research and Manufacturers of America, *Comment on Proposed Pediatric Testing Rule*, No. 97N-0165, Nov. 13, 1997.

⁵⁹*Chevron U.S.A., Inc. v. National Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

⁶⁰5 U.S.C. § 706(2)(A) (1994).

⁶¹*Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402 (1971).

⁶²*See* *United States v. An Article of Drug, Bacto-Unidisk*, 394 U.S. 784 (1969).

⁶³*United States v. Nova Scotia Foods Prods.*, 568 F.2d 240, 246 (2d. Cir. 1977) (quoting *Mourning v. Family Publications Svcs., Inc.*, 411 U.S. 356, 369 (1973)).

⁶⁴*See* *Pharmaceutical Manufacturers Ass’n. v. Food and Drug Administration*, 484 F.

its claims to statutory authorization fails this lenient test.

1. “FALSE AND MISLEADING IN ANY PARTICULAR”

In support of its rule, FDA first argues that drugs and biological products that do not contain adequate pediatric labeling based on FDA-approved pediatric studies are misbranded under §§ 502(a) and 502(f) of the FDCA. A drug is misbranded under § 502(a) if its labeling is “false or misleading in any particular.”⁶⁵ Although “false” and “misleading” conjure images of affirmatively false labeling, the FDCA’s definition of the term is broad, including not only affirmative falsehoods but also material omissions. As § 201(n) states, a product’ label is misleading if “fails to reveal facts material... with respect to consequences which may result” either from the use of the product suggested by the label or from “the use of the [product] under such conditions of use as are customary or usual.”⁶⁶ FDA’s regulations interpret this to allow FDA to require adequate directions for every use “for which the drug is commonly used.”⁶⁷ Because “there is extensive evidence that drugs for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness have not been established in children,... FDA may therefore consider pediatric

Supp. 1179, 1183 (D. Del. 1980).

⁶⁵21 U.S.C. §352(a) (1994).

⁶⁶21 U.S.C. §321(n) (1994).

⁶⁷21 C.F.R. §201.5 (1999).

use to be ‘customary or usual’ or ‘commonly used.’”⁶⁸

Several objections might be made to FDA’s claims. First, some of the legislative history of § 201(n) suggests that it was not designed to operate as broadly as FDA alleges. In particular, the House Committee Report on the 1938 Act appears to suggest that the provision was designed to require a disclaimer qualifying claims to curative effects that are not unequivocally supported by the scientific evidence. As the Report states, the provision is designed to satisfy consumers’ “right to know, when it is a fact, that the representations of curative value have only a narrow and limited support, and if the label fails to reveal that fact, which is a material fact in light of the representations made, then the labeling may be regarded as misleading. However, the misleading character of the label may be corrected by an appropriate qualifying statement revealing this material fact.”⁶⁹ If this accurately stated the legislative intent of § 201(n), pediatric labeling would not be authorized, since it is not designed to qualify an affirmative curative claim for pediatric patients; indeed, the rule allows FDA to require pediatric testing even for drugs for which pediatric use has been expressly disclaimed. But the House Report does not conclusively demonstrate that § 201(n) precludes FDA from requiring more than qualifying disclaimers for “narrowly” supported curative claims. Although the Report’s analysis might exhaustively describe FDA’s authority to require facts that are material in light of the “representations” made on the labeling, it does not speak at all to FDA’s textually granted authority to require facts that are material in

⁶⁸Pediatric Testing Rule, 63 Fed. Reg. at 43,907.

⁶⁹H. R. REP. NO. 2139, 75th Cong. (1938), *reprinted in* CHARLES WESLEY DUNN, FEDERAL FOOD, DRUG, & COSMETIC ACT 822 (1938).

light of the product’s “customary and usual *use*.”⁷⁰ This clearly demonstrates that the committee’s description of § 201(n)’s aims was illustrative rather than exhaustive and that FDA’s statutory authority transcends the single application suggested by the Report.⁷¹

A second objection to the 1998 rule is that FDA’s judgment that drugs without pediatric labeling are misbranded is “arbitrary and capricious” given that it has historically approved such drugs. Because estoppel does not lie against the government,⁷² this argument is essentially a claim that, as a matter of statutory interpretation, FDA’s long-standing practice of declining to consider drugs without pediatric labeling misbranded constitutes extrinsic evidence that those products are not misbranded according to the statutory definition. While this argument may be clever, it essentially constitutes a claim that past agency practice is binding through canons of statutory interpretation. Although a few old administrative law cases came close to accepting this rationale,⁷³ it conflicts quite severely with the modern understanding that agencies can alter their policies and interpretations as long as they provide sufficient explanation to the parties.⁷⁴ Thus, the agency’s past approval of these drugs does not preclude it from deeming them misbranded in light of a new policy judgment about the importance of pediatric testing.

Finally, challengers to the FDA rule might dispute FDA’s conclusion that par-

⁷⁰21 U.S.C. §321(n) (1994).

⁷¹*See also* Pharmaceutical Manufacturers Ass’n. v. Food and Drug Administration, 484 F. Supp. 1179, 1184 (D. Del. 1980).

⁷²*See* Office of Personnel Management v. Richmond, 496 U.S. 414 (1990).

⁷³*See* Packard Motor Car v. National Labor Relations Board, 330 U.S. 485 (1947).

⁷⁴*See* Shaw’s Supermarkets, Inc. v. National Labor Relations Board, 884 F.2d 34 (1st Cir. 1989) (Breyer, C.J.).

ticular drugs are “customar[il]y or usual[ly]” used in pediatric patients. Courts interpreting § 201(n) have, however, given FDA wide latitude to define uses that are customary or usual. In *National Nutritional Foods Association v. Novitch*,⁷⁵ for example, the district court refused to grant an injunction against FDA’s requirement that certain protein products with fewer than 400 calories per day contain a label warning of the risk of serious injury or death. In ruling for the government, the court stated that even if the product were not marketed for weight reduction, the “agency was entitled to find reasonably that weight reduction was a ‘customary or usual use’ of the product by reason of the fact that it was ‘used for such purposes with some frequency.’”⁷⁶ The courts’ broad interpretation appears to validate FDA’s regulation, which defines “customary or usual” uses as those that are “common.”⁷⁷ In sum, FDA’s 1998 Pediatric Testing rule is authorized under §§ 502(a) and 201(n) of the FDCA.

2. “ADEQUATE DIRECTIONS FOR USE”

FDA also claims that it can require pediatric testing because products without pediatric labeling do not have “adequate directions for use” and are therefore misbranded.⁷⁸ In subsequent regulations, FDA has interpreted “adequate directions for use” to mean “directions under which the layman can use a drug safely

⁷⁵589 F. Supp. 798 (S.D.N.Y. 1984).

⁷⁶*Id.* at 801.

⁷⁷21 C.F.R. 201.5 (1999).

⁷⁸21 U.S.C. §352(f) (1994).

and for the purposes for which it is intended.”⁷⁹ In this context, FDA defines “intent” as the “objective intent of the persons legally responsible for the labeling of drugs.”⁸⁰ Objective intent may be shown by “labeling claims, advertising matter, or oral or written statements by [the manufacturer].”⁸¹ In addition, however, “if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.”⁸² In other words, purpose and knowledge (actual or constructive) on the part of the manufacturer satisfy the requirement of intentionality as interpreted by FDA. Pursuant to these regulations, FDA claims that manufacturers who market drugs that are widely used in pediatric patients have either actual or constructive knowledge of these uses. As a result, the products are misbranded because they do not contain directions for pediatric use.⁸³

FDA’s interpretation of “intent” might be compared to the statutory definition of the term in the context of the definition of drugs and medical devices. According to the FDCA, drugs and medical devices are defined as products that are “intended to affect the structure or any function of the body.”⁸⁴ Courts interpreting these provisions have deeply divided over the question whether in-

⁷⁹21 C.F.R. §201.5 (1999).

⁸⁰21 C.F.R. §201.128 (1999).

⁸¹*Id.*

⁸²*Id.*

⁸³*See* Proposed Pediatric Testing Rule, 62 Fed. Reg. 43,900, 43,907 (1997).

⁸⁴21 U.S.C. §§ 321(g)(1)(C), 321(h)(3) (1994).

tentionality for the purposes of defining a drug or medical device can be proven absent claims by the manufacturer about the product’s use. Several courts have acknowledged that intent can be inferred from evidence extrinsic to the manufacturer’s representations. For example, the Second Circuit has stated that “the intended use of a product may be determined from its label, accompanying label, promotional material, advertising, and *any other relevant source*.”⁸⁵ Other courts have concurred, albeit in dictum.⁸⁶ By contrast, other courts have rejected the suggestion that intent can be inferred from evidence extrinsic to the label. Most prominently, a panel of the Fourth Circuit in *Brown & Williamson Tobacco Corp. v. Food and Drug Administration*⁸⁷ insisted that tobacco products were not drugs within the meaning of the statute because “no court has ever found that a product is ‘intended for use’ or ‘intended to affect’ within the meaning of the [FDCA] absent manufacturer claims as to that product’s use.”⁸⁸ Given the deep division between the courts, and the salience of the political issue of FDA’s authority to regulate tobacco, this issue may well be resolved when the Supreme Court reviews *Brown & Williamson* this Term.

Even if the Supreme Court agrees with the Fourth Circuit and rejects extrinsic evidence of intent, FDA’s interpretation of intent in the context of § 502(f) is

⁸⁵United States v. Article of 216 Cartoned Bottles, “Sudden Change,” 409 F.2d 734, 739 (2d. Cir. 1969) (emphasis added); *see also* United States v. Ten Cartons Ener-B Vitamin B-12, 72 F.3d 285, 287 (2d. Cir. 1995) (“An article can be a drug under 21 U.S.C. § 321(g)(1)(C) for reasons other than claims made in the label or labeling, such as ‘method of intake.’”).

⁸⁶*See, e.g.*, United States v. 250 Jars U.S. Fancy Pure Honey, 218 F. Supp. 208, 211 (E.D. Mich. 1963) (To determine intended use, “a court is not limited to the labels on such articles or to the labeling which accompanies it, but may look at all relevant sources.”).

⁸⁷153 F.3d 155 (4th Cir. 1999), *cert. granted* 119 S. Ct. 1495 (1999) (reversing *Coyne Beahm, Inc. v. United States Food & Drug Administration*, 966 F. Supp. 1374 (M.D.N.C. 1997)).

⁸⁸*Brown & Williamson*, 153 F.3d at 163 (quoting *CoyneBeahm*, 966 F. Supp. at 1390).

likely to survive. Indeed, although there is a canon in statutory interpretation that the same word will be given the same meaning throughout the statute, this canon should yield to the principle of deference to agencies' interpretation of their own regulations. As the Supreme Court has stated, an agency's interpretation of its own regulations is controlling unless an "alternative reading is compelled by the regulation's plain language or by other indications of the Secretary's intent at the time of the regulation's promulgation."⁸⁹ Clearly, the division among the courts on the issue suggests that there is no "plain meaning" of the term "intent." There is also no evidence that the agency, at the time of promulgating 21 C.F.R. § 201.5, intended to limit term "intent" to the manufacturer's express purpose as evidenced by the label. Thus, the agency's interpretation of intent as purpose or knowledge (actual or constructive) should withstand judicial scrutiny even if the Supreme Court rejects a similar interpretation of the FDCA's provisions defining drugs and medical devices.

Deference to the agency's interpretation is further warranted by two additional facts. First, courts should not interfere with agency interpretations of its own regulations where the regulation concerns "a complex and highly technical regulatory program" such as FDA's regulation of drug labeling.⁹⁰ Drug labeling requires a delicate balance between public safety and industry responsibility, and the agency's ability to strike the proper balance without second-guessing on the part of the courts is quite essential to the successful accomplishment of

⁸⁹*Gardenbring v. Jenkins*, 485 U.S. 415, 430 (1988); *see also* *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 513 (1994) ("[Courts] must give substantial deference to an agency's interpretation of its own regulations.");

⁹⁰*Thomas Jefferson Univ.*, 512 U.S. at 512 (1994) (quoting *Pauley v. BethEnergy Mines*, 501 U.S. 680, 697 (1991)).

this balance. Second, deference is even more appropriate where, as here, the agency’s interpretation has declined to exercise its full statutory authority. Indeed, because § 502(f) does not expressly require that the “adequate directions for use” requirement be limited to intended uses, FDA could, as a strictly legal matter, have required adequate directions for *any* use of the product—even one that the manufacturer had no reason to know would occur. Thus, while FDA’s interpretation of its own regulations may ultimately not conform to the courts’ interpretation of the FDCA, its interpretation deserves greater deference as a voluntary limitation on agency power rather than an unauthorized aggrandizement.

3. “SUGGESTED” USE IS DANGEROUS OR NOT RECOGNIZED AS SAFE

FDA also claims authority to require pediatric testing on the grounds that (1) pediatric use is a “new drug” that is not generally recognized “as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof”⁹¹ and (2) that the drug is misbranded because it is “dangerous to health” when used in a manner “prescribed, recommended, or suggested in the labeling.”⁹²

Several issues arise in conjunction with FDA’s claims. First, one might ask whether FDA is authorized to deem a drug “new” on the basis of a new use

⁹¹21 U.S.C. §321(p) (1994).

⁹²21 U.S.C. §352(j) (1994).

rather than a new chemical entity.⁹³ Courts, however, have upheld FDA’s authority in this regard, holding that FDA can consider a drug “new” if it is marketed for a new use or if it involves a new method of utilization.⁹⁴ Second, one might ask whether FDA can deem a drug “dangerous to health” in the absence of evidence of actual toxicity. Although some drugs have resulted in toxicities in pediatric patients, the vast majority of them simply have not been tested for children. However, the statute clearly states that a drug may be deemed misbranded if it is “dangerous to health *when used in the dosage or manner, or with the frequency or duration* prescribed, recommended, or suggested in the labeling thereof.”⁹⁵ Clearly, a drug labeled for adults would be dangerous if prescribed in the dosages recommended for adults.

Thus, the dispositive question is not whether pediatric uses are new or whether they are dangerous to health; rather, the ultimate question is whether the manufacturer “prescribed, recommended, or suggested” pediatric use of the drug. FDA argues that it is entitled to “consider pediatric use to be ‘suggested’ in a drug’s labeling even where such use is not expressly recommended or is even disclaimed.”⁹⁶ This argument is unpersuasive. Unlike the agency’s authority

⁹³See 21 C.F.R. § 310.3(h)(5) (1999) (The newness of a drug may arise from “the newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.”).

⁹⁴See *United States v. Article of Drug Labeled Colchicine*, 442 F. Supp. 1236, 1243 (S.D.N.Y. 1978) (citing 21 C.F.R. § 310.3(h)(5) as supporting FDA’s contention that phenytoin in time-release capsule form is a new drug even though phenytoin in single dosage form is generally recognized as safe and effective); *Merrit Corp. v. Folsom*, 165 F. Supp. 418, 421 (D.D.C. 1958) (“The newness of a drug... may arise by reason of, among others, a new or different recommended use for the drug, or a new or different duration of administration, even though the same drug may not be a new drug when used in another disease or other duration of administration”).

⁹⁵21 U.S.C. § 321(p) (1994).

⁹⁶Pediatric Testing Rule, 63 Fed. Reg. 66,632–66,658 (1999).

under §§ 502(a) and 201(n), which allows the agency to consider the “customary or usual” use of the product, §§ 201(p) and 502(j) explicitly limit the agency’s authority to the representations made by the drug manufacturer. Although there is some ambiguity as to the precise scope of a “prescription, recommendation, or suggestion,” the plain language of the statute requires at least that there be an affirmative statement of some kind. The interpretations of §§ 201(p) and 352(j) by the courts confirm this view. All of the courts that have affirmed libel actions against misbranded drugs under § 502(j) have found that the drug was misbranded because of an affirmative suggestion that the drug be used in a certain way that is dangerous to health.⁹⁷ Similarly, actions under § 201(p) have been affirmed by the courts only where the drug’s manufacturer made a representation suggesting a use for a product that was not generally recognized as safe.⁹⁸ It appears clear, then, that the courts’ interpretation of the statute is not so broad as to allow FDA to regulate drugs whose safety and efficacy are uncertain only under conditions about which the manufacturer makes no representations or claims.⁹⁹

⁹⁷*See, e.g.*, *United States v. Torigian Laboratories, Inc.*, 577 F. Supp. 1514, 1525 (E.D.N.Y. 1984) (finding that the drug’s labeling — which contained the term “intraocular lens” — suggested that the lenses be used for surgery, and that the surgical use of non-sterile lenses was a danger to the public health); *United States v. Relaxacizor, Inc.*, 340 F. Supp. 943 (C.D. Cal. 1970) (holding that electrical muscle stimulator was misbranded because failed to warn of possible side-effects under expressly prescribed conditions of use); *United States v. Lanpar Co.*, 293 F. Supp. 147, 154 (N.D. Tex. 1968) (holding that drug was misbranded because dangerous to health when used to fight obesity in the manner prescribed by the accompanying promotional material).

⁹⁸*See, e.g.*, *Merrit Corp. v. Folsom*, 165 F. Supp. 418 (D.D.C. 1958) (; *United States v. Article of Drug Labeled “Quick-O-Ver,”* 274 F. Supp. 443 (D. Md. 1967) (holding that hangover potion was not recognized as safe for labeled use because of the potential side effects of ingredient ephedrine).

⁹⁹This provides little consolation to manufacturers challenging the FDA’s 1998 rule, however, since FDA clearly does have authority to deem a drug misbranded based on the failure to disclose facts material to the drug’s “customary or usual” use under §§ 502(a) and 201(n). *See supra*.

Moreover, even if the manufacturer could “suggest” a use through omission rather than representation, the law clearly does not allow FDA to regulate manufacturers that have expressly disclaimed pediatric use on the labeling or other accompanying information. As courts have held, a manufacturer who warns about the dangers of a prescribed use cannot be held liable for misbranding under § 201(p).¹⁰⁰ By corollary, manufacturers who have disclaimed a particular use should not be liable for misbranding. Thus, FDA is unjustified in asserting that manufacturers have “prescribed, recommended, or suggested” pediatric use sufficient to confer jurisdiction under §§ 201(p) and 502(j).

B. FDA AND CONGRESS—PEDIATRIC TESTING REQUIREMENTS AS A SOLUTION TO “MARKET FAILURE”

The 1998 rule is authorized under two of the three provisions discussed above. In addition, however, the rule’s validity also depends on its relationship to Congress’s simultaneous efforts to resolve the problem of pediatric testing. Indeed, if the FDAMA’s incentive provisions were clearly intended to supplant or preempt the mandatory provisions proposed by FDA, then the rule’s legitimacy would be in grave doubt under the first prong of *Chevron*.¹⁰¹ The legislative his-

¹⁰⁰See *Fellows v. USV Pharmaceutical Corp.*, 502 F. Supp. 297, 301 (D. Md. 1980) (holding manufacturer cannot be liable for misbranding if it provides warning about the risks of prescribed use).

¹⁰¹See *Chevron U.S.A., Inc. v. National Resources Defense Council, Inc.*, 467 U.S. 837, 842 - 43 (1984) (“If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.”). Inquiry into congressional intent must be particularly searching where an agency is attempting

tory of the FDAMA, however, does not support the contention that the FDAMA clearly repudiated the mandatory testing approach taken in the 1998 rule. What the legislative history does make clear, however, is that Congress intended the FDAMA's incentive provisions to be the first line of attack in attempting to ensure more comprehensive pediatric information. Congress intended the 1998 rule to "complement" the incentive scheme as a policy of last resort. Thus, the rule's application should be limited to those circumstances in which Congress's incentive scheme has demonstrably failed.

FDA's rulemaking occurred in front of a complicated legislative backdrop. Like FDA, Congress was deeply concerned about the problem of inadequate pediatric testing. Yet the legislative solution they proposed remained deeply wedded to the idea of incentive structures rather than regulatory mandates. Indeed, just 45 days before FDA proposed the Pediatric Testing Rule, the Senate Labor and Human Resources Committee had referred the FDAMA, which contained provisions creating market-based incentives for drug manufacturers to conduct voluntary pediatric tests, to the full Senate.¹⁰² By the time FDA finalized its rule in December 1998, the FDAMA's pediatric testing incentives had been in place for over a year. The legislative history of the FDAMA's pediatric testing provisions demonstrates how Congress intended to use market-based incentives as the primary solution to inadequate pediatric testing.

to expand its authority, arguably beyond statutory limits. *See* *ACLU v. FCC*, 823 F.2d 1554, 1567 n. 32 (D.C. Cir. 1987) ("When an agency's assertion of power into new arenas is under attack... courts should perform a close and searching analysis of congressional intent, remaining skeptical of the proposition that Congress did not speak to such a fundamental issue.").

¹⁰²*See* 143 CONG. REC. D631 (daily ed. June 18, 1997).

Although the FDAMA was not passed until 1997, the pediatric testing provisions that it incorporated were proposed over five years earlier. In 1992, the same year that FDA proposed its 1994 rule, federal legislators led by Senator Nancy Landon Kassebaum (R-KS) proposed the Better Pharmaceuticals for Children Act to create incentives to induce pediatric testing by manufacturers. The bill, which was modeled after existing market incentive provisions in the FDCA,¹⁰³ proposed to extend “6 months’ marketing exclusivity for drug products for which FDA-approved pediatric studies are conducted” in order to create incentives for pediatric testing by manufacturers.¹⁰⁴ Given that Senator Kassebaum introduced the bill only several weeks before the end of the legislative session, it was by her own admission not a firm proposal but rather “a vehicle for discussion in coming months.”¹⁰⁵

Senator Kassebaum vastly underestimated the amount of time her proposed discussion would take. Over the course of the next four years, she tirelessly reiterated her concerns about the paucity of pediatric testing. Yet each time, the dialogue she began ended without passage of a resolution. She reintroduced the bill in the next Congress in 1994,¹⁰⁶ and her House colleague, Rep. Mike Kreidler of Washington, introduced parallel legislation in the House of Representatives.¹⁰⁷ Both bills died in committee.

In 1996, she proposed the bill again, this time picking up the key support of

¹⁰³See 28 U.S.C. § 355(j)(4)(D) (1994).

¹⁰⁴138 CONG. REC. S16,998 (daily ed. Oct. 5, 1992, statement of Sen. Kassebaum) (introducing The Better Pharmaceuticals for Children Act, S. 3337, 102nd Cong. (1992)).

¹⁰⁵*Id.* at S16,999.

¹⁰⁶See 140 CONG. REC. S4165 (daily ed. Apr. 12, 1994, statement of Sen. Kassebaum) (introducing The Better Pharmaceuticals for Children Act, S. 2010, 103rd Cong. (1994)).

¹⁰⁷See 140 CONG. REC. E935 (daily ed. May 16, 1994, statement of Rep. Kreidler).

Senator Edward Kennedy (D-MA), the ranking minority member on the Senate Labor and Human Resources Committee.¹⁰⁸ In committee, the bill was incorporated as part of The Food and Drug Administration Regulatory Reform Act of 1995 (“the 1995 Reform Act”), which sought broad-based reforms of the regulatory process at FDA.¹⁰⁹ Although the 1995 Reform Act was referred out of committee with broad bipartisan support,¹¹⁰ it faced opposition among powerful senators, including Senator Kennedy. Senator Kennedy objected to the provisions which created mandatory, but shortened, product review time frames for approving some priority drugs on the grounds that they would “cripple the FDA.”¹¹¹ In addition, he objected to the provisions which allowed for third-party expert review of some drugs on the grounds that they would “turn [FDA’s regulatory] functions over to private industry.”¹¹² Although Kennedy admitted that FDA could be more effective, he refused to allow his colleagues to “destroy the safeguards protecting the American people” from unsafe food and drugs.¹¹³ Ultimately, because of senators’ inability to resolve their acrimonious disagreements, no action was taken on the bill before the legislative session ended, and supporters vowed to take the issue up again in the next session.¹¹⁴ In the next session, Senator Jeffords, picking up the mantle for Senator Kassebaum, who had decided not to run for reelection, introduced the FDAMA,

¹⁰⁸See 142 CONG. REC. S11,992 (daily ed. Sept. 30, 1996, statement of Sen. Kassebaum) (introducing The Better Pharmaceuticals for Children Act, S. 2178, 104th Cong. (1996)); see also *id.* (daily ed. Sept. 30, 1996, statement of Sen. Dodd).

¹⁰⁹S. Res. 1477, 104th Cong. (1996).

¹¹⁰See 142 CONG. REC. D288 (daily ed. Mar. 28, 1996).

¹¹¹142 CONG. REC. S3203 (daily ed. Mar. 29, 1996, statement of Sen. Kennedy).

¹¹²*Id.*

¹¹³*Id.* at S3204.

¹¹⁴See 142 CONG. REC. S12,150 (daily ed. Oct. 2, 1996, statement of Sen. Kassebaum); 142 CONG. REC. S12,053 (daily ed. Oct. 1, 1996, statement of Sen. Hatch).

which, like the 1995 Reform Act, included the provisions of original the Better Pharmaceuticals for Children Act.¹¹⁵ This time, the legislation passed, partly because of the changes that were made to the bill to satisfy Senator Kennedy, and partly because of Senator Kennedy's desire to compromise in order to secure reauthorization of the Prescription Drug User Fee Act of 1992, which would have expired in 1997. Thus, after a long legislative journey, the provisions of the Better Pharmaceuticals for Children Act were finally passed in 1997 as § 505(A) of the amended FDCA.¹¹⁶

In the final debate over the FDAMA, legislators who were aware of FDA's Proposed Pediatric Testing rule struggled to reconcile it with Congress's seemingly inconsistent approach. Members' attitudes toward the FDA rule differed markedly. Some supporters of the FDAMA—especially Republicans—appear to have supported incentives and not mandates. For example, in the Senate Labor and Human Resources Committee's report on the FDAMA, which was issued before FDA's proposed rule, the committee commended FDA for attempting to solve the problem of inadequate pediatric testing “by using its authority to approve labeling based upon the known pharmacokinetics of the drug, *as opposed to requiring pediatric clinical trials for efficacy*.”¹¹⁷ Likewise, Representative Bliley, the main House sponsor of the FDAMA, expressed concern about FDA's implementation of the law's pediatric provisions, emphasizing that the purpose of the provision was to induce clinical testing through market incentives rather

¹¹⁵See 143 CONG. REC. S5342 (daily ed. Jun. 5, 1997, statement of Sen. Jeffords) (introducing The Food and Drug Administration Modernization Act of 1997, S. 830, 105th Cong. (1997) (enacted)).

¹¹⁶Pub. L. No. 105-115, § 111, 111 Stat. 2305 (1997) (codified at 21 U.S.C. § 355(a) (1997)).

¹¹⁷S. REP. 105-43, at 51-52 (1997) (emphasis added).

than mandates.¹¹⁸

Even those members who supported FDA's efforts to require pediatric testing portrayed the Proposed Pediatric Testing rule as a supplement to the FDAMA's incentive provisions. For example, Rep. Henry Waxman (D-CA) emphasized in his speech supporting the FDAMA that its pediatric exclusivity provisions "complement[ed] the FDA's recent regulations."¹¹⁹ Likewise, Senator Mike Dewine (R-OH), speaking after FDA's rule was proposed, applauded FDA and argued that the FDAMA's pediatric testing provisions were intended to "work with FDA's regulation."¹²⁰

In sum, when Congress passed the FDAMA in 1997, legislators were deeply divided on its consistency with FDA's mandatory approach. Although some members were quite reluctant to acknowledge the validity or wisdom of the FDA rule, most legislators clearly did not intend the FDAMA to preempt FDA's mandatory testing rule. Rather, they intended the FDAMA's incentive provisions to complement FDA's mandatory provisions.

IV. FDA IMPLEMENTATION OF § 505(A) AND THE 1998 RULE—USING THE STICK AS A LAST RESORT WHEN THE CARROT FAILS

As FDA moves forward in implementing both its rule and the FDAMA pro-

¹¹⁸See *Implementation of FDA Modernization: Hearing Before the Subcomm. on Health of the House Comm. on Commerce*, 105th Cong. (1997), 1998 WL 18089104.

¹¹⁹143 CONG. REC. E10,534 (daily ed. Nov. 9, 1997, statement of Rep. Waxman).

¹²⁰143 CONG. REC. S9823 (daily ed. Sept. 24, 1997, statement of Rep. Dewine).

visions as complementary provisions, it should be mindful of the delicate balance between the incentive- and mandate-based approaches. As of the time of this paper, FDA has yet to issue proposed regulations to implement § 505(A)’s provisions; it has only published an updated guidance that serves as an interim interpretation (“Guidance document”).¹²¹ FDA plans to promulgate an updated Guidance detailing the interrelationship between the 1998 rule and the pediatric exclusivity provisions of § 505(A) in the next few months.¹²² This final Part offers prescriptions for ensuring that these regulations truly complement the mandatory testing requirement, as Congress intended.

As noted above, FDA should implement the 1998 Pediatric Testing rule as a solution to market failure rather than as a generalized regulatory mandate. In order to let the market incentive structure have a chance to work, FDA should use its power under the 1998 rule only in cases when the market incentives have demonstrably failed. Otherwise, if FDA preemptively imposes testing requirements before the market incentives have had an opportunity to work—as it appears to have done in regard to its 1994 rule—it will unjustifiably undermine the market solution intended by Congress.

There are two conditions under which the market incentive provisions created by the FDAMA will systematically underproduce pediatric information. Only in these situations where the “carrot” is inadequate should FDA resort to the

¹²¹See Center for Drug Evaluation, Food and Drug Administration, *Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505(A) of the Federal Food, Drug, and Cosmetic Act*, Sept. 1999 [hereinafter *Guidance for Industry*].

¹²²Telephone Interview with Terrie Crescenzi, Project Manager, Pediatric Implementation Team, Center for Drug Evaluation and Research, Food and Drug Administration (Jan. 27, 2000).

“stick” of mandatory testing. First, because the incentive provisions created by § 505(A) of the FDAMA apply only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act¹²³ and the Orphan Drug Act,¹²⁴ they will simply have no effect on drugs that are not covered by these laws. This includes many biologics, antibiotics, and, obviously, off-patent products.¹²⁵ Thus, if FDA finds that pediatric information regarding these products is necessary to the pediatric population, then it must do so through the mandatory provisions of the Pediatric Testing rule. This presumably is not inconsistent with Congress’s intent: By limiting the coverage of § 505(A)’s incentive provisions, the Congress declined to provide a market-based solution for these types of products, presumably leaving the field open for regulation by the agency.

Second, the inevitable truth about market-based solutions is that the production of some information will always be economically inefficient under a given incentive regime. Faced with the prospect of six-months’ exclusivity extension, manufacturers will only conduct tests on drugs for which the benefit of the exclusivity exceeds the cost of the testing. The result of this cost-benefit analysis may not always correspond to the drug’s importance to pediatric populations. In particular, there are two types of drugs for which the incentives created by § 505(A) may be inadequate. One potential problem is drugs that “are greatly needed to treat pediatric patients, but that have smaller markets.”¹²⁶ Because

¹²³Pub. L. No. 98-417, 99 Stat. 1585 (1984).

¹²⁴Pub. L. No. 97-414, 96 Stat. 2049 (1983).

¹²⁵See Pediatric Testing Rule, 63 Fed. Reg. 66,632, 66,633 (1997).

¹²⁶*Id.*

the market is small, the value of the additional market exclusivity may be small, making the additional tests unattractive from a cost-benefit standpoint. Another potential fear is that manufacturers will have an inadequate incentive to conduct studies in neonates. As noted in Part I, above, information in neonates is almost universally unavailable, largely because the market incentive is insufficient given that studies on neonates are often extremely expensive. Thus, where the market incentives are insufficient to induce manufacturers to conduct studies (1) for small-market drugs or (2) in small populations such as neonates, it is appropriate for FDA to resort to the mandatory framework set out in the 1998 rule.

In sum, the FDA rule and the FDAMA's provisions should be truly complementary. The FDAMA's six-month market exclusivity provision provides a significant incentive for manufacturers voluntarily to submit pediatric studies for FDA approval. Only when this market incentive is insufficient—i.e., for drugs that (1) are very important to a small number of pediatric patients but that are not profitable for marketing to pediatric populations or (2) are off-patent—should FDA exercise its authority to require testing and force the manufacturer to conduct FDA-approved studies to ensure safety and effectiveness for children.

IV. CONCLUSION—FDA IN A NEW REGULATORY ENVIRONMENT

FDA is unique in its regulatory power, both in terms of the breadth of

its statutory powers and in the deference that it receives from courts in exercising those powers. The case of pediatric testing is no different: Unsurprisingly, FDA's vast expansion of power is authorized by the statute and would be validated by any court in which it were to be challenged. But the 1998 Pediatric Testing rule is also situated within the new regulatory culture ushered in by the Republican Congress. This culture is driven by incentives rather than mandates, markets rather than regulation. It is evidenced not only in § 505(A) of the FDAMA but also in Congress's other deregulatory legislation.¹²⁷ Within this new regulatory environment, the position of FDA's Pediatric Testing rule is rather tenuous. As FDA implements its 1998 Pediatric rule, in light of the FDAMA's pediatric exclusivity provisions, FDA should—both out of institutional self-protection and in deference to the sovereign will of legislature—exercise its wide discretion carefully so as not to disrupt the market structure intended by Congress.

¹²⁷ See, e.g., TRYON A. BRENNAN & DONALD M. BERWICK, NEW RULES: REGULATION, MARKETS, AND THE QUALITY OF AMERICAN HEALTH CARE 12 - 13 (1996) (describing the Republicans' return to a deregulatory regime based on market incentives, repudiating the activist regulation of the 1980s).